REMARKS

A. Regarding the Amendments

By the present amendment, Applicants have amended claims 1-24 and 33, 34 and 38-42, as set forth in the attached "Version With Markings To Show Changes Made;" canceled claims 25-32, 35-37 and 43-59; and added new claims 60-66. As amended, the claims are supported by the specification and the original claims. The foregoing amendments reflect cancellation without prejudice of claims drawn to non-elected matter, use of Applicants' preferred terminology and organization, and address issues raised in the Office Action mailed October 18, 2002 (Paper No. 12), as discussed below. Thus, upon entry of the amendments, claims 1-24, 33, 34, 38-42 and 60-66 will be pending.

Independent claims 1 and 33 have been amended to recite that the isolated HLA pan DR-binding peptide be one of two classes, each of which broadly comprises a peptide of up to about 30 amino acid residues. In the first class, the peptide includes a "core sequence" flanked at either end (e.g., the amino- and carboxy-termini) by at least two amino acid residues. The core sequence is recited to be one of LSTLVVNKI, LSTLVLNRL, LSEKKISSI, LEDPYILLV, FQDAYVLLS, LTTEAVVAD, FLTTEAVVA, or LTTAEVVVT. See specification, paragraph [000123] and Table 1 for support for the "core sequence." Additionally, this first class of peptide comprises a naturally occurring amino acid sequence. The second class concerns peptides that comprise amino acid sequences having at least about 70% sequence identity to those of the first class. Support for this class is found in the specification at, for example, paragraph [00044], and claim 5 as originally filed.

Claims 1-24 have been amended to change the term "substantially pure peptide" to "isolated peptide," as suggested in Paper No. 12. Support for this change is found in the specification at, for example, paragraph [00041].

The term "naturally occurring" in claims 1 and 3, as amended, is clear, in that means that the amino acid sequence is one that exists in a naturally occurring protein. The specification is

replete with support for this term. For example, see specification paragraphs [00043] and [00044] and Table 1. Claim 3 has been further amended to reflect the amendment of claim 1, from which it directly depends and which relates to two alternate classes of peptides, one of which concerns peptide fragments that have amino acid sequences found in stress proteins that occur in nature, and the other of which comprises peptide fragments the amino acid sequences of which have at least 70% sequence identity with those of the first class. Finally, the language of claim 3 has been amended to reflect a Markush grouping.

As amended, claim 4 now depends from claim 3, and concerns peptide fragments from bacterial heat shock proteins that are mycobacterial in origin. Support for bacterial heat shock proteins is found in the specification at paragraph [00040] and claim 11 as originally filed.

Claims 5-9 have been amended to conform to the amended terminology of claim 1, from which they each directly or indirectly depend, and to cancel SEQ ID NOs. 4 and 10 from the claims' respective Markush groups.

The amendments in claims 10-16, as well as those in claims 22-24, 34-37, and 39-42, are also simply conforming the amended terminology of the claims from which they depend.

The change in claim 17 from "about 10" to "13" conforms the language of the claim to that of claim 1, as amended. "About" has been added before "30" simply to clarify that the term originally presented in the claim also applies to the upper end of the range. A similar change has also been made to claims 18 and 19.

In claim 20, the term "residue" has been added to reflect that in a peptide, as a result of the formation of the peptide bonds between amino acids, the amino acids inherently become "amino acid residues."

Claim 21 has been streamlined but still reflects that the peptide contains a conservative amino acid substitution. Conservative substitutions are described in the specification at paragraph [00045].

Claims 34-42, as amended, now lack the term "immunomodulating," as this term was superfluous in such composition claim.

In claim 38, "substantially pure" has been changed to "isolated" and SEQ ID NOs. 4 and 10 have been deleted from the Markush group.

New claims 60-64 depend from claim 1, and thus concern isolated peptides of the invention. New claims 65 and 66 depend from claim 33, and concern formulations.

Specifically, support for new claim 60, specifically the term "mammalian heat shock protein" may be found in the specification, for example, at paragraph [00038] and in claim 14 as originally filed. New claims 61 and 62 are supported in the specification, for example, at paragraph [00042]. Claim 63 is supported in the specification, for example, at paragraph [00044] for express support. Additionally, new claim 64 is supported in the specification at, for example, paragraph [00044]. Finally, new composition claims 65 and 66 are supported in the specification at, for example, paragraphs [00100], [00102], and [00103].

The amendments herein do not introduce new matter, therefore their entry at this stage is proper, and Applicants respectfully request reconsideration of the claimed invention, as amended, in view of the following comments regarding various issues raised in Paper No. 12.

B. Restriction Requirement

Applicants acknowledge the finality of the restriction between Group I and Groups IV and V made in Paper No. 12. In view of this, Applicants have elected to cancel claims drawn to non-elected inventions, without prejudice to their prosecution in one or more related applications.

C. Rejection Under 35 U.S.C. § 112

Applicants respectfully traverse the rejection of claims 1-24 and 33-42 under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to point out and distinctly claim the subject matter of the invention.

It is alleged in Paper No. 12 that the term "substantially pure peptide" is indefinite and that one of skill in the art "cannot define the metes and bounds of such a limitation." It is noted that, though all the claims of the invention are addressed by this rejection, only claims 2-23, 33 and 38 possess the term "substantially pure peptide."

The Examiner's attention is respectfully drawn to paragraph [00042] on pages 11-12, in which the term "substantially pure peptide" is defined. As set forth in this paragraph, a substantially pure peptide is "typically pure when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated." However, it is also stated in that paragraph that the peptide may be up to 99%, by weight, and will have a sequence which is a fragment of the sequence as set forth in SEQ ID NO:1 or SEQ ID NO:13. It is also noted that the paragraph states that purity can be measured by any appropriate method, such as by column chromatography, polyacrylamide gel electrophoresis, or by HPLC analysis. Those of skill in the art would know of additional methods of purification.

As there is a clear definition as to the metes and bounds of the term "substantially pure peptide," it is respectfully submitted that one of skill in the art would be able to identify a peptide of the claim and therefore the claim is not vague or indefinite. However, in the interest of advancing prosecution, the term has been amended to "isolated peptide." As such, the rejection is respectfully submitted as moot and withdrawal is respectfully requested.

Additionally, the specification is objected to and claim 21 is rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite with respect to recitation of the term "chain of amino acids 'similar size, charge and/or polarity.'" Applicants respectfully disagree. It is respectfully submitted, as is set forth in MPEP 2111.01, that words of a claim are given their plain meaning, unless otherwise indicated in the specification. Applicants respectfully submit that in this application, "similar size" is meant as its plain meaning and that one of skill in the art would understand use of the term.

It is alleged in Paper No. 12 that it is vague and indefinite whether the term "similar size" refers to same weight, same ring structure, or approximate weight. It is respectfully submitted that size refers to none of these characteristics. Size, weight and structure are three different physical characteristics of a chain of amino acids. "Size" is defined by Webster's Dictionary as "physical magnitude, extent, or bulk[;] relative or proportionate dimensions[;] relative aggregate amount or number[;] considerable proportions [;] bigness." Therefore it is respectfully submitted that one of skill in the art would know that the language "similar size" in the claim refers to other amino acid chains similar in proportion. One of skill in the art would not think that "similar size" refers to weight or ring structure and would know that the metes and bounds of a "similar size" refer to similar in relative dimensions. Accordingly, the term "similar size" is not vague or indefinite. However, in order to advance prosecution of the application, claim 21 has been amended to remove the allegedly indefinite term. Withdrawal of the rejection is therefore respectfully requested.

Similarly, the specification is objected to and claims 3 and 4 are rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite with respect to recitation of the term "conserved." It is alleged in Paper No. 12 that one of skill in the art "cannot define the metes and bounds of such a limitation."

The Examiner's attention is respectfully drawn to paragraph [00037] on page 10, in which an explanation is given of heat shock protein conservation. As set forth in this paragraph, conservation among families is high for heat shock proteins. Therefore, the term "conserved" would not be indefinite to one of skill in the art. It is stated in the specification that a stress protein includes other proteins, muteins, analogs, and variants thereof having at least 35% to 55%, preferably 55% to 75%, and most preferably 75% to 85% amino acid identity. (Specification, page 10, paragraph [00037].) Additionally, when claims 3 and 4 are read in light of claim 1, from which they depend, it is clear that the claimed sequence has a conservation of at least about 70%. This percent identity indicates to one of skill in the art the percentage of

conservation disclosed by the present application. Therefore one of skill in the art would not find the term "conserved" vague or indefinite.

Therefore, claims 1-24 and 33-42 meet the definiteness requirement of 35 U.S.C. §112, second paragraph. Accordingly, removal of the rejections is requested.

D. Rejection Under 35 U.S.C. § 102

Applicants respectfully traverse the rejection of claims 1-19, 21, 24 and 33-39 under 35 U.S.C. 102(b) as allegedly anticipated by Thompson (WIPO international publication WO 96/10039). Paper No. 12 states that this published patent application discloses a peptide fragment identical to SEQ ID NO. 4. Applicants respectfully submit that since the claims, as amended, no longer include a peptide having the amino acid sequence of SEQ ID NO. 4, the basis for this rejection has been obviated. Accordingly, Applicants respectfully submit that this rejection should be withdrawn.

Additionally, Applicants respectfully traverse the rejection of claims 1-17, 21, 24 and 33-39 under 35 U.S.C. 102(b) as allegedly anticipated by Anderton (WIPO international publication WO 95/25744). It is alleged in Paper No. 12 that Anderton discloses a peptide fragment identical to SEQ ID NO. 2. Applicants respectfully traverse, because each element of the claimed invention is not disclosed in Anderton. Figure 13 of Anderton reports an amino acid alignment between three mammalian (i.e., human, rat, and mouse) and one bacterial (i.e., *Mycobacterium tuberculosis*) hsp60 proteins. No fragments of the full-length *M. tuberculosis* protein are reported in that figure. Moreover, the peptide reported in Anderton that contains amino acid residues 256-270 of *M. tuberculosis* hsp65 is not identical to SEQ ID NO. 2 of the instant invention. Indeed, SEQ ID NO. 2 comprises amino acid residues 254-268 of *M. tuberculosis* hsp65.

Also, peptides within the scope of claim 1, as amended, are different from the peptides of Anderton. Specifically, for example, the core sequence LSTLVVNKI is found in SEQ ID NO. 2

of the instant invention, as well as in the peptide that contains amino acid residues 256-270 reported in Anderton. This core sequence begins at amino acid position 257 of *M. tuberculosis* hsp65. However, claim 1, as amended, requires that a peptide within the scope of the claim as amended contain at least two amino acid residues at each end of the core sequence. Thus, at the amino terminus, amino acids corresponding to amino acid positions 255 and 256 must be included. Anderton does not describe inclusion of these residues.

For these reasons, Applicants respectfully submit that there is not strict identity between the disclosure of Anderton and the claimed invention. As neither Thompson nor Anderton describes all elements of the claimed invention, withdrawal of the 35 U.S.C. § 102(b) rejection is respectfully requested.

E. Rejection Under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1-24 and 33-42 under 35 U.S.C. 103(a) as allegedly unpatentable over Anderton (WIPO international publication WO 95/25744) in view of Srivastava (U.S. Pat. No. 6,455,503) and Russell-Jones (U.S. Pat. No. 5,928,644) and Guichard (PNAS USA, vol. 991, p. 9765-9769.). Applicants respectfully traverse for two reasons. First, the instant invention demonstrates unexpected results. Second, the legal standard for analyses under 35 U.S.C. § 103 in view of a combination of publications, *i.e.*, that the publications must provide both a motivation for their combination and a reasonable expectation of success, is not satisfied.

Turning first to unexpected results, as described in Example 2 of the instant application, it had previously been reported that a peptide made up on amino acids 256-270 of *M. tuberculosis* hsp65 could induce protection in a rat model of adjuvant arthritis. However, in children suffering from JIA, Applicants discovered that their T cells were not induced by the bacterial peptide, as measured by T cell proliferation and cytokine production assay. In contrast, a peptide

having the amino acid sequence of SEQ ID NO. 2 of the instant invention was found to induce T cell responses in these same human patients, as measured by the same assays.

The cited combination of publications also fails to satisfy the controlling legal standard. Simply put, there is nothing in the cited publications to suggest their combination, or that the cited combination would lead an ordinarily skilled artisan to have a reasonable expectation of success. Anderton concerns certain bacterial peptides reported to be useful in protecting against or treating an inflammatory disease, such as an autoimmune disease, e.g., arthritis. In contrast, Srivastava reports certain vaccines containing stress protein-peptide complexes useful in stimulating cytotoxic T cell responses against cells infected with a pre-selected intracellular pathogen. There is no teaching or suggestion in either of these references that the peptides of Anderton be used in the complexes of Srivastava, or vice versa. Moreover, Russell-Jones concerns possible T cell epitopes derived from the integral membrane protein TraT from *E. coli* complexed with various immunogens. There is no reason why an ordinarily skilled artisan would seek to combine the disclosures of the cited U.S. patents, as one concerns vaccines for intracellular pathogens, whereas the other relates T cell epitopes from *E. coli*. Applicants respectfully submit nothing in the cited publications suggests that *E. coli* is an intracellular pathogen, or that the TraT protein of *E. coli* is a stress protein. Even without addressing the Guichard publication, it is clear that there is no motivation to combine the cited publications, either in their disclosures or in the art in general. This alone is reason enough to justify withdrawal of the instant rejection.

For these reasons, Applicants respectfully request withdrawal of the 35 U.S.C. § 103 rejection.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1-24, 33, 34, 38-42 and 60-66 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 677-1456. Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: February 18, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Currently Amended) [A substantially pure] An isolated HLA pan DR-binding peptide comprising [a fragment of] a stress protein fragment that binds to [one or more] a MHC class II molecule[s], wherein the fragment is up to about 30 amino acid residues in length and (i) comprises a core sequence flanked at either end by at least two amino acids, wherein the core sequence has an amino acid sequence selected from the group consisting of LSTLVVNKI, LSTLVLNRL, LSEKKISSI, LEDPYILLV, FQDAYVLLS, LTTEAVVAD, FLTTEAVVA, and LTTAEVVVT, and wherein the fragment comprises a naturally occurring amino acid sequence, or (ii) comprises an amino acid sequence having at least about 70% sequence identity to a fragment of part (i).

2. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 1, wherein the peptide binds to HLADR1, DR4, and DR7.

3. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 1, wherein the naturally occurring [peptide comprises an] amino acid sequence [that] is selected from an amino acid sequence from a [conserved between] human heat shock protein and a bacterial heat shock protein[s].

4. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim [1] 3, wherein the bacterial heat shock protein [peptide comprises an amino acid sequence that] is a [conserved between human and] mycobacterial heat shock protein[s].

5. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 1, wherein the amino acid sequence of the peptide is at least 70% identical to [a] an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 3, [4,] 5, 6, 7, 8, and 9 [and 10].

6. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 5, wherein the amino acid sequence of the peptide is at least 80% identical to [a] an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 3, [4,] 5, 6, 7, 8, and 9 [and 10].

7. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 5, wherein the amino acid sequence of the peptide is at least 90% identical to [a] an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 3, [4,] 5, 6, 7, 8, and 9 [and 10].

8. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 1, wherein the amino acid sequence of the peptide is at least 95% identical to [a] an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 3, [4,] 5, 6, 7, 8, and 9 [and 10].

9. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 5, wherein the amino acid sequence of the peptide has [a] an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 3, [4,] 5, 6, 7, 8, and 9 [and 10].

10. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 1, wherein the stress protein is a heat shock protein.

11. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 10, wherein the heat shock protein is a bacterial heat shock protein.

12. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 10, wherein the heat shock protein is a mycobacterium species heat shock protein.

13. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 12, wherein the mycobacterium species heat shock protein is hsp65 [or hsp60].

14. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 10, wherein the heat shock protein is a mammalian heat shock protein.

15. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 14, wherein the mammalian heat shock protein is a human heat shock protein.

16. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 15, wherein the human heat shock protein is human hsp60.

17. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 1, wherein the fragment is [about 10] 13 to about 30 amino acids in length.

18. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 17, wherein the fragment is about 15 to about 25 amino acids in length.

19. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 17, wherein the fragment is about 15 to about 20 amino acids in length.

20. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 1, wherein the peptide has one or more D- amino acid[s] residues.

21. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 5[,] that contains a conservative amino acid substitution at [wherein] at least one [or more] amino acid position in [of] the peptide[s selected from the group consisting of SEQ ID NOs: 2, 3, 4, 5, 6, 7, 8, 9 and 10 has been substituted by one or more amino acid having a similar size, charge and/or polarity].

22. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 1, wherein the peptide is covalently linked to an adjuvant.

23. (Currently Amended) [The substantially pure] An isolated peptide [of] according to claim 22, wherein the adjuvant is keyhole limpet hemocyanin, bovine serum albumin, human serum albumin, or isologous IgG.

24. (Currently Amended) A pharmaceutical composition[,] comprising a peptide [of] according to claim 1 in a pharmaceutically acceptable carrier.

33. (Currently Amended) [An immunomodulating] A composition [for use in treating or preventing an inflammatory disorder] comprising a pharmaceutically acceptable carrier and [a substantially pure] an isolated peptide comprising a fragment of a stress protein that binds to [one or more] a MHC class II molecule[s in a pharmaceutically acceptable carrier], wherein the fragment is up to about 30 amino acid residues in length and (i) comprises a core sequence flanked at either end by at least two amino acids, wherein the core sequence has an amino acid sequence selected from the group consisting of LSTLVVNKI, LSTLVLNRL, LSEKKISSI, LEDPYILLV, FQDAYVLLS, LTTEAVVAD, FLTTEAVVA, and LTTAEVVVT, and wherein the fragment comprises a naturally occurring amino acid sequence, or (ii) comprises an amino acid sequence having at least about 70% sequence identity to a fragment of part (i).

34. (Currently Amended) [The immunomodulating] A composition [of] according to claim 33, wherein the fragment binds to at least one molecule selected from the group consisting of HLADR1, DR4, and DR7.

38. (Currently Amended) [The immunomodulating] A composition [of] according to claim 34, wherein the [substantially pure] isolated peptide has [a] an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 3, [4,] 5, 6, 7, 8, and 9 [and 10].

39. (Currently Amended) [The immunomodulating] A composition [of] according to claim 34, further comprising a biological response modifier.

40. (Currently Amended) [The immunomodulating] A composition [of] according to claim 39, wherein the biological response modifier is selected from the group consisting of a cytokine, a chemokine, a hormone, a steroid, and an interleukin.

41. (Currently Amended) [The immunomodulating] A composition [of] according to claim 40, wherein the biological response modifier is an interferon.

42. (Currently Amended) [The immunomodulating] A composition [of] according to claim 39, wherein the biological response modifier is selected from the group consisting of IL-1(α or β), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, GM-CSF, M-CSF, G-CSF, LIF, LT, TGF-β, γ-IFN, TNF-α, BCGF, CD2, [or] and ICAM.